REMARKS

The Examiner has objected to the Specification "because page 1, line 12 contains blank space." The Examiner has also stated that "Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 120". The Specification has been amended to delete the blank space on page 1, line 12 and updated to contain specific reference to prior a applications and issued patent. Accordingly, Applicants request that the instant application receive the benefit of an earlier filing date and the objection to the Specification be withdrawn.

Claims 1 and 32-46 are pending in the application.

Rejection of Claims 1 and 32-46 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 1 and 32-46 under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Specifically, the Examiner states that the:

> "[c]laims are vague and indefinite because of claim recitation, 'mature T cells'. In 9/17/03 response, applicants indicated that the specification recites the term in page 6, line 30, and explain that a mature T cell is a terminally differentiated T cell that migrates out of the thymus and circulates in the blood stream (Response, page 6). This definition agrees with the original disclosure which recites mature T cells following immature T cells in a markush group, and meets the plain meaning for the term, *i.e.* terminally differentiated as oppose to undifferentiated (stem and progenitor cells), thus is acceptable. However, applicants later appear to argue that transformed T cells are not considered as mature T cells (Response, page 8). This is confusing because a transformed mature T cell is still a mature T cell, would not change to an immature T cell. Particularly considering claim 37 is drawn to treating an HIV virus infected T cells (transformed), the exclusion would be contradict the claims. Thus, in view of applicants' argument, the metes and bounds of the claims are unclear. Further, the specification fails to specifically redefine the term, and if applicants intend to exclude a transformed mature T cell from the claimed term, it would represent a departure from the term as originally recited, thus, would introduce new matter to the disclosure."
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> "Claims are vague and indefinite because of claim recitation, a 'submitogenic amount of an anti-CD3 antibody'. However, except disclosing a specific dose in a working example, the specification fails to teach what dosing range is considered as submitogenic, what dosing range the term embraces or excludes, thus the metes and bounds of the claims are unclear. In 9/17/03 response, applicants indicated that the specification teaches a specific amount of anti-CD3 antibody (1 μg/ml) in page 33, lines 35-39, and recites 'submitogenic

> doses of anti-CD3' in page 43, line 17. However, it is noted in U.S. patent 6,352,694 by applicants, June, *et al.* teach the dosing range of anti-CD3 antibody for inducing a population of T cells to proliferate, for example, in column 31, line 33, they teach, "WITH OKT3, THE OPTIMAL CONCENTRATION WAS DETERMINED TO BE TYPICALLY IN THE RANGE OF 0.1 TO 10 MiCROGRAMS PER MILLILITER", wherein the specified submitogenic amount in the instant application is at exact mid-point of the dosing range that induces T cell proliferation. Since the same dose would induce T cell proliferation, and is submitogenic, it is further unclear, what the claimed term embraces or excludes, thus, the metes and bounds of the claims cannot be readily determined."

Applicants respectfully traverse these rejections. With respect to the use of the phrase "mature T cells" and the Examiner's rejection, it is Applicants position that the Examiner has misunderstood the meaning of a "transformed cell line" as recited in the September 17, 2003 response on page 8. Applicants have used the phrase "transformed cell line" in terms of its art recognized meaning to be a cell line maintained in culture that has acquired a malignant phenotype, *i.e.,* cancerous or dedifferentiated. Since cancerous cells lose their differentiated phenotype and more closely resemble immature, undifferentiated cells, Applicants submit that one skilled in the art would recognize that a mature T cell is clearly distinguishable from either an immature and/or transformed T cell.

With respect to the Examiner's rejection of Applicants' recitation of "a submitogenic amount of an anti-CD3 antibody", Applicants submit that although June, *et al.* teach that the optimal concentration to induce T cells to ***proliferate*** is between 0.1 to 10 micrograms per milliliter, June, *et al.* actually state at column 31, lines 29-31, "[f]or any anti-CD3 antibody, the optimal concentration to be coated on tissue culture flasks ***must be determined experimentally***." Therefore, although June, *et al.* teaches a dose of an anti-CD3 antibody to induce T cells to ***proliferate*** that overlaps with the dose of anti-CD3 that Applicants teach which is submitogenic, Applicants submit that one skilled in the art recognizes that with each and every antibody, each type of cell, and each type of culture system, the exact dosage of antibody that will cause a particular cell type to proliferate or to not proliferate under the specific conditions being utilized will vary and must be determined using routine experimentation. Therefore, the metes and bounds are clearly defined by the phrase "a submitogenic amount of an anti-CD3 antibody". Applicants therefore respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §112, second paragraph.

Rejection of Claims 1 and 32-46 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 1 and 32-46 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or which is most nearly connected, to make and/or use the invention.

Specifically, the Examiner states that:

> Kwon, *et al* do use mature peripheral T cells (PBMC, column 20, lines 53-55), not immature T cells, for contacting of anti-CD3 and anti-CD28 antibodies. On the other hand, the claimed invention does not have limitation on times of exposure, thus encompasses the condition taught by Kwon, *et al, i.e.* repeated exposure to anti-CD3 and anti-CD28. It is also noted Kwon, *et al* do recite a high dose of anti-CD3, however, the amount used in contacting PBMC was 1 ug/ml soluble anti-CD3 mAb (column 17, line 31), apparently the term "high" is a relative one, thus they did use *submitogenic* amount as defined by the applicants 9/17/03 response. Accordingly, the arguments are not persuasive.
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> Applicants then argue that example 6 of the instant application describes experiments performed on Jurkat cells, which are of a transformed cell line and subject to AICD, and examples 1-5 utilize primary mature T cells, that are not subject to AICD.
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> In response, it is noted that Jurkat cells are terminally differentiated mature T cells though transformed, and have been widely used in the art for studying characteristics of T cells. The brief recitation of "mature" T cells in the original disclosure appears to be used as contrast to immature and it does not exclude Jurkat cells. It is additionally noted that in examples one through six, the original disclosure refers to cells used as "resting" and "activated", either they are primary or Jurkat line, accordingly, it appears that not only the Jurkat cells are subject to AICD but the regular mature T cells are also subject to AICD.

Applicants respectfully traverse this rejection and reiterate that Kwon, *et al.* (US Patent No. 6,303,121) teaches that activated T cells which are ***reactivated*** multiple times with ***high doses*** of anti-CD3 can become resistant to the effects of CD28, and anti-CD28. The teachings of Kwon, *et al.*, with respect to anti-CD3 inducing apoptosis, are therefore specific to ***mitogenic amounts*** of anti-CD3. Applicants point the Examiner to column 21, lines 9-49 where Kwon, *et al.* describe the effect of repeated engagement of the T cell receptor (TCR) by exposure to "multiple", "high doses" of anti-CD3 and refer to the fact under these particular experimental conditions, this amount of anti-CD3 added to the culture was proliferative (*i.e.,* mitogenic). As stated at column 21, lines 9-49 of Kwon, *et al.*:

> It was also discovered that after ***multiple cycles of reactivation*** of previously activated cells by a ***high dose*** of soluble anti-CD3, significant cell death was seen. This was true even in the presence of substantial amounts of anti-CD28. These results are consistent with recent reports by others that TCR reengagement induced apoptosis ***after a strong initial proliferative response to antigen***, and large concentrations of IL-2 for cell cycle progression. One of the consequences of repeated *in vitro* activation, especially following an exposure to high dose IL-2, is the gradual loss of responsiveness to CD28 co-stimulation. The repeated TCR activation, a condition for cell death, instead, induced 4-1BB expression. It is therefore believed that continuous reactivation may cause irreversible damage, leading to apotosis, even in the presence of CD28 signaling, and that co-engagement of 4-1BB with CD28 could prevent the anti-CD3 reactivation driven apoptosis. The effects of 4-1BB on cell proliferative activity during *in vitro* repeated activity by anti-CD3 and anti-CD28 was studied. The PHA-activated T cells, after IL-2 stimulation for 10 days until the T cell blasts returned to smaller cell sizes, were continuously reactivated by anti-CD3 and anti-CD28 with or without 4-1BB co-engagement. After each of three cycles of reactivation, the cells were reactivated again by anti-CD3 in 96-well plates coated with serially diluted anti-CD28 from 0.01 to 10 μg/ml with or without an additional 10 μg/ml of anti-4-1BB.
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> ***The cells were examined for proliferative activity by measuring [^{3}H] thymidine incorporation. As the number of reactivation cycles proceeded, cells became less responsive to anti-CD28, resulting in a lower maximum proliferation plateau***, even with saturated anti-CD28 concentrations. After the third cycle re-activation, T cells barely responded to anti-CD28 alone. The 4-1BB co-engagement with CD28, however, exerted a dramatic effect in overcoming the defective proliferation, as well as fully restoring maximal plateaus of expression. The 4-1BB signal alone failed to demonstrate a strong level of expression. The 4-1BB effects were blocked by the functional antagonist, 4-1BBFc, the soluble form of 4-1BB when it was included in reactivation, indicating the specificity of anti-4-1BB. (emphasis added)

In light of the teachings of the present specification and since Kwon, *et al.* teach that the anti-CD3 initially caused the T cells to proliferate and that it was only after repeated TCR engagement that T cells underwent apoptosis, the use of the submitogenic amounts of anti-CD3 antibodies as claimed, to protect a T cell from programmed cell death, is clearly enabled.

With respect to the Examiner's assertion that Jurkat cells are not excluded from the claims as pending, Applicants submit that a Jurkat cell line is a ***T-cell leukemia cell line***, *i.e.*, a cancerous cell line, *i.e.*, a transformed cell line, *i.e.*, immature. As such, the recitation of ***mature*** in the pending claims excludes Jurkat cells. Applicants also traverse the assertion by the Examiner that both Jurkat cells and mature T cells are subject to AICD. Applicants reiterate that AICD is activation-induced T cell death (AICD), known in the art to occur in ***immature T cells***

and also in some ***transformed***, *e.g.*, cancerous, cell lines and ***T cell hybridomas***. AICD does not result from contact of a mature, resting T cell obtained from a subject with anti-CD3 antibodies.

The Examiner further cites Lenardo, *et al.* (US Patent No 6,083,503), and states that the invention as claimed encompasses the situation taught by Lenardo, *et al.*

Applicants reiterate that the teachings of Lenardo, *et al.* do not in any way suggest that the instant claimed methods are inoperable. Lenardo, *et al.* teach a specific effect of IL-2 exposure on T cells *in vitro* prior to antigen exposure, wherein subsequent re-exposure of the T cells to antigen within 2-3 days *in vitro* leads to T cell death. As set forth at column 13, lines 24-38) of Lenardo, *et al.*:

> The basic concept of the present therapeutic approach is very simple. Disease-causing T cells are ***first challenged by immunization, which causes the activated T cells to express high affinity IL-2 receptors and to begin producing and secreting IL-2.*** When the cells are expressing high levels of IL-2 receptor, additional human IL-2 is infused to very efficiently drive all the activated cells into cycle. ***The cells under the influence of IL-2 are then caused to undergo apoptosis by re-immunization with antigenic peptide or protein***. Further, if the antigen is capable of stimulating sufficient IL-2 production, it is not necessary to administer exogenous IL-2. In either case, the timing of rechallenge is important--it must occur within a short interval such as 2-3 days after the first stimulus when cells bear the IL-2 receptor and are responding to exogenous or endogenous IL-2. (emphasis added)

Lenardo, *et al.* further teaches that "the effects of IL-2 wear off 2-3 days after IL-2 is no longer present, hence rechallenge must occur within that period"(column 12, line 27-29). Since the effects of IL-2 exposure wear off relatively quickly, given the guidance of the specification and the knowledge of one skilled in the art, one so skilled could practice the claimed methods without inadvertently inducing cell death in cells which may have been previously exposed to IL-2.

The Examiner reiterates '[w]ith respect to the superantigens, Applicants again argue that cited references discussing specific situations, do not say that the present invention is not enabled. In response, since the claims encompass the said specific situations, they are not fully enabled with the scope." and "[w]ith respect to the therapeutic aspect of the invention, applicants argue that the art is not as unpredictable as those cited references, arguing details of each reference, and concluded that the teaching of the references have no bearing on the instant claims." The Examiner continues,

> [t]he art of record is silent and the specification fails to teach the circumstance necessary to introduce these generalized mature T cells into a subject, or once they are activated, or differentiated, the *ex vivo* observed protective effect would remain, thus, the specification fails to provide an enabling disclosure to guide the practice of the invention. Applicants are reminded that 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970). In the instant case, the specification provides no evidence with respect to how the treated T cells would behave *in vivo*, the functionality and pharmacokinetics of these T cells, and conditions for using such cells.

Applicants respectfully traverse this rejection. With respect to the teachings of Johnson, *et al.* (US 5,968,514) and superantigens cited by the Examiner (column 4, lines 26-44), Applicants reiterate that the cited teachings are highly speculative and are not supported by experimental evidence. As set forth at column 4, lines 26-53 of Johnson, *et al.*:

> Superantigens are also associated with retroviruses such as mouse mammary tumor virus (MMTV), and ***possibly*** human immunodeficiency virus (HIV), the virus responsible for AIDS. It has recently been reported that two exogenous strains of MMTV encode retroviral superantigens in the open reading frames (ORFs) of the 3' Long Terminal Repeat (LTR) of the viral genome (Pullen, A. M., Y. Choi, E. Kushnir, J. Kappler, P. Marrack [1992] J. Exp. Med. 175:41-47; Choi, Y., P. Marrack, J. Kappler [1992] J. Exp. Med. 175:847-851). There is ***preliminary evidence*** that the HIV genome ***may*** also encode a superantigen. It has been suggested that an HIV superantigen ***may*** target a sub-population of CD4.sup.+ T cells for HIV viral replication (Laurence, J., A. S. Hodtsev, D. N. Posnett [1992] Nature 358:255-259). HIV infection also results in the programmed cell death of CD4sup+ T cells (apoptosis), both in vitro and in vivo, ***possibly*** as a result of an HIV protein with superantigen properties (Gougeon, M-L., L. Montagnier [1993] Science 260:1269-1270). Feline immunodeficiency virus (FIV) is a lentivirus which has been described extensively in the literature. See, for example, Kiyomasu, Takahiro, et al. (1991) "Identification of Feline Immunodeficiency Virus rev Gene Activity" Journal of Virology 65(8):4539-4542, and references cited therein. There has also been speculation that the human spumaretrovirus (HSRV) expresses a superantigen ("Molecular Biology of the Human Spumavirus," in Human Retroviruses, B. R. Cullen, ed., Oxford University Press, Oxford and New York, 1993, pp. 205-206). (emphasis added)

With respect to the teachings of Lenardo, *et al.* (US 6,083,503) and the teaching of Lynch, *et al.* (US 6,015,559) relating to superantigens, Applicants reiterate that Lenardo, *et al.* teach that bacterial Staphylococcus superantigen induced T cell PCD in mice. Furthermore, as discussed above, the teachings of Lenardo, *et al.* teach these specific ***in vivo*** effects in T cells

previously exposed to IL-2. Furthermore, Applicants teach at least at Example 7, page 41, lines 26 through page 42, lines 27 that increased BCL-X_L protects T cells from apoptosis in the absence of IL-2 (page 42, lines 26-27).

Lynch, *et al.* are merely referencing the work of Scott, *et al.* (1993 *J. Immunol.* 150:664). Scott, *et al.* teach that ***in mouse models of autoimmune disease*** (Lupus), "The present study demonstrates that there is no global defect in peripheral T cell deletion or anergy in lupus-prone mice to the superantigen SEB. Although additional Ag would need to be studied, these experiments raise the possibility that some reported ***tolerance defects in lupus-prone strains may reflect excessive B cell responses*** to relatively normal T cell signals." (Abstract). Lynch, *et al.* refer to the Scott, *et al.* reference and speculate that "[b]y promoting T cell apoptosis, TNF could account for the reported ability of certain antigens and superantigens to cause peripheral T cell deletion in ***lpr*** mice (Scott, *et al.*, *J. Immunol.* 150:664, 1993)." (column 30, lines 25-28).

Both of the phenomena reported by Lenardo, *et al.* and Lynch, *et al.* occur ***in vivo***. No evidence is presented that apoptosis would occur as a result of contact of the superantigens under controlled conditions ***ex vivo***, as claimed, *i.e.,* a method for protecting a mature T cell from cell death, comprising contacting the T cell *ex vivo* with at least two agents. The claimed methods are performed under controlled conditions, to produce the desired inhibition of cell death of the T cell isolated from an individual. Applicants have presented evidence that a variety of superantigens can protect a mature T cell from cell death when utilized in the claimed methods, and have enabled a representative number of species for the claimed genus. Moreover, the determination of additional superantigens appropriate for use in the claimed methods is within the ability of one of ordinary skill in the art through no more than routine experimentation.

Regarding the concerns of the Examiner with respect to reintroducing into the subject the treated cells, Applicants again argue that the Examiner has failed to provide teachings in the art that indicate that the methods of the present invention would not work and thus lack enablement. Furthermore, Applicants submit that based on the teachings and guidelines of the present invention, in combination with the ***knowledge of one of skill in the art*** at the time the application was filed, methods of introducing the cells treated according to the present invention into the subject are routine to one skilled in the art. As stated in *Forman*, "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance." *Ex parte Forman*, 230 USPQ 546, 547 (Bd. App. 1986). As also pointed out by the Federal Circuit

in *Northern Telecom, Inc. v. Datapoint Corp.*, 15 USPQ 2d 1321 (1990), "[i]t is not fatal if some experimentation is needed, for the patent document is not intended to be a production specification." 15 USPQ 2d at 1329. See, also *In re Brana*, 34 USPQ 2d 1436 (Fed. Cir. 1995).

The Examiner also rejects claims 1 and 32-46 under 35 U.S.C. §112, first paragraph, because

> [t]hese claims read on using any combination of two agents as recited in claims 1 and 39, for example a combination of CD28 ligand and an ionomycin. However, the specification and the numerous cited art of record (see sections following) have shown the necessary presence of or pre-exposure to the anti-CD3 antibody such as those shown in figure 2 and experiment 2. The specification provides no evidence that in the absence of the anti-CD3, any other combination would result in T cell protection. In fact, the specification shows that anti-CD28 could enhance bcl-x expression caused by T cell exposure to anti-CD3 (fig. 3), but anti-CD28 alone did not induce detectable BCI-XL as shown in figure 5. Since the specification teaches that the increased BCI-XL is the key to T cell survival, in the absence of evidence to the contrary, the invention as claimed do not appear to be enabled.

Applicants traverse this rejection and submit that the methods of the currently pending claims require ***that at least 2 agents*** be selected from the group consisting of an anti-CD28 antibody, a sub-mitogenic amount of an anti-CD3 antibody, an anti-CD2 antibody, a CD28 ligand, interleukin-2 (IL-2), ionomycin, A23187, phorbol-12, 13-dibutyrate, a lectin and a superantigen. The Examiner is correct in that Figure 5 shows that ***CD28 alone*** did not induce detectable amounts of BCL-XL, however a combination of at least 2 agents did induce BCL-XL protein production. Therefore, the claims are enabled.

With respect to the Examiner's assertion that the numerous cited references indicate that anti-CD3 is required and that the specification "provides no evidence that in the absence of anti-CD3, any other combination would result in T cell protection", Applicants submit that none of the cited references teach a method to protect a T cell from apoptosis in the presence or absence of anti-CD3 and therefore the reliance on these references is inappropriate.

In conclusion, Applicants submit that the specification is enabling for the claimed methods, *i.e.*, protecting a mature T cell from cell death, comprising contacting the T cell *ex vivo* with at least two agents selected from the group consisting of an anti-CD28 antibody, a sub-mitogenic amount of an anti-CD3 antibody, an anti-CD2 antibody, a CD28 ligand, interleukin-2 (IL-2), ionomycin, A23187, phorbol-12, 13-dibutyrate, a lectin and a superantigen, wherein the agent increases BCL-X_L protein level in the T cell such that the T cell is protected from cell death. In

view of all of the above, reconsideration and withdrawal of the §112, first paragraph rejections is requested.

Rejection of Claims 1 and 32-35 and 37-38 Under 35 U.S.C. §012(e)

The Examiner has rejected claims 1, 32-35, and 37-38 under 35 U.S.C. §102(e) as being anticipated by June, *et al.* (US 6,352,694, and 6,534,055). Specifically, the Examiner states that "June, *et al.* teach a method comprising contacting T cells *in vitro* with an anti-CD3 antibody (*e.g.* step a of claims 1 and 17 of the cited '694 patent), and an anti-CD28 antibody (step b of claim 1 of the cited '694 patent) or an anti-CD2 antibody, preferably T11.1 (column 5, line 65-column 6, lines 12) or PHA (column 3, line 20), wherein the anti-CD3 is OKT3 (column 5, line 62)."

The Examiner continues:

> The teachings of '694 patent as detailed above and in the previous Office action paper #11 are also disclosed in the newly cited '055 patent."
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> First, it is noted that although June, *et al.* do not use the term 'submitogenic', they do teach the dosing range of anti-CD3 antibody ***for inducing a population of T cells to proliferate***. For example, in column 31, line 33, they teach, 'With OKT3, the optimal concentration was determined to be typically in the range of 0.1 to 10 micrograms per milliliter', wherein the specified dose in the instant application is 1 μg/ml, at exact midpoint of the taught dosing range, thus, the teaching of June, *et al.* meet claim limitation.
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> Second, the method step of cited patent meets claim limitation. Although the effect of increasing Bcl-X was not disclosed in the cited patents, as indicated in the previous action, that merely discovering and claiming a new benefit to an old process cannot render the process again patentable. (emphasis added)

Applicants respectfully traverse this rejection. As stated above, it is understood by those skilled in the art that the appropriate amount of an antibody that induces a specific cellular response, *e.g.,* mitogenic or submitogenic, will vary depending on multiple conditions and thus must be experimentally determined. Although the amount of antibody recited by June, *et al.* (US 6,352,694, and 6,534,055) and the present application overlap, the currently pending claims require the dose of anti-CD3 to be ***submitogenic***. In addition, as described above and as the Examiner noted the amount of anti-CD3 utilized by June, *et al.* was mitogenic, *i.e.,* causes cells to ***proliferate***.

Furthermore, as the Examiner is well aware, for a prior art reference to anticipate a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. ***June, et al. teach methods for inducing a population of T cells to proliferate.*** In contrast, the pending claims are directed to methods of ***protecting a mature T cell from cell death*** comprising contacting the T cell with at least two agents, wherein the agent increases BCL-X_L protein level in the T cell such that the T cell is protected from cell death. June, *et al.* do not provide any teaching or suggestion whatsoever that a T cell treated with the claimed agents would increase BCL-X_L protein levels. Moreover, June, *et al.* ***do not teach or suggest methods of inhibiting T cell death*** as is claimed in the instant application. Therefore, for the reasons set forth above, June, *et al.* (US 6,352,694) and June, *et al.* (6,534,055), either alone or in combination, do not teach or suggest each and every limitation of the claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejections.

Rejection of Claims 1 and 32-38 Under 35 U.S.C. §102

The Examiner has rejected claims 1, 35, 36, 37, and 38 under 35 U.S.C. 102(b) as being anticipated by Groux, *et al.* (*J Exp Med* 1992:175:331-340). Specifically, the Examiner states that:

> Groux, *et al.* teach a method comprising contacting human matured T cells with an anti-CD3 antibody at a submitogenic amount (1 μg/ml, 2nd paragraph, left column, page 332), plus anti-CD28, PHA, PWA, and superantigen ShB (Figures 1 & 2), wherein the T cells are from either HIV seropositive (infected) or seronegative patients. Groux, *et al.* go on to teach that anti-CD28 prevented T cell apoptosis (*e.g.* abstract). Accordingly, Groux, *et al.* anticipate the instant claims.

The Examiner has also rejected claims 1, 32, and 38 under 35 U.S.C. 102(b) as being anticipated by Wolf, *et al.* (*Eur J Immunol* 1994;24:1410-17). Specifically, the Examiner states that:

> Wolf, *et al.* teach a method comprising contacting human matured resting T cells with an anti-CD3 antibody (OKT3) at a submitogenic amount (*e.g.* abstract and fig. 1), plus anti-CD28 or anti-CD2 (table 2 and figure 3), wherein the combined administration of anti-CD3 and one of the co-stimulatory molecule anti-CD28 or anti-CD2 could prevent anti-CD3 induced T cell anergy. Wolf, *et al.* go on to teach that anti-CD3 induced T cell anergy is associated with increased cell death

(e.g. § 3.2, page 1412) and prevented by the co-stimulatory molecule (§ 3.4, page 1414). Accordingly, Wolf, *et al.* anticipate instant claims.

The Examiner further rejects claims 1, 32 and 38 under 35 U.S.C. 102(e) as being anticipated by Lederman, *et al.* (US 6,610,294). Specifically, the Examiner states that:

> Lederman, *et al.* teach a method comprising contacting mature human T cells (column 34, lines 46-55) with anti-CD3 and PBD (column 27, lines 56-59), wherein the anti-CD3 is OKT3 and coated on a culture surface, although Lederman, *et al.* do not specify the amount used, considering the common practice in the art using a dosing range of 0.1-10 μg/ml for coating surface, and 1 μg/ml for stimulating T cells as evidenced by Groux, *et al.* and June, *et al.* the amount is assumed to be submitogenic in the absence of evidence to the contrary. Accordingly, Lederman, *et al.* anticipate instant claims.

The Examiner has also rejected claims 1, 32-35, 37, and 38 under 35 U.S.C. 102(e) as being anticipated by Gary, *et al.* (US 5,883,223). Specifically, the Examiner states that:

> [t]he applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.
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> Gary, *et al.* teach a method comprising contacting T cells in vitro with an anti-CD3 (OKT3, column 4, line 50) at a submitogenic amount (column 20, line 55) and an anti-CD28 antibody (example 1) or an anti-CD2 antibody, preferably T11.1 (column 5, line 65-column 6, lines 12), or IL-2 and PHA (fig. 1), or B7-1 and B7-2 (column 6, lines 26-27), wherein the T cells could be obtained from HIV infected patients (fig. 15). Accordingly, Gary, *et al.* anticipate instant claims.

The Examiner further rejects claims 1, 32-38 under 35 U.S.C. 102(e) as being anticipated by Thompson, *et al.* (US 6,685,941). Specifically, the Examiner states that:

> [t]he applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.
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> Thompson, *et al.* teach a method comprising contacting T cells in vitro with an anti-CD3 (OKT3) at a submitogenic amount and anti-CD28 antibody

(*e.g.* table 13) or IL-2 and PHA (table 3), or B7-1 and B7-2, or superantigen SEB (fig. 16), wherein the T cells could be obtained from HIV infected patients. Accordingly, Thompson, *et al.* anticipate instant claims.

The Examiner has further rejected claims 1, and 32-38 under 35 U.S.C. 102(f) "because the applicant did not invent the claimed subject matter." The Examiner continues "[t]his application has a different inventive entity as that of US Patent 5, 883,223; 6,352,694; 6,534,055; and 6,685,941 but the subject matter is anticipated by the cited patents, it is unclear with regard to who is the real inventor."

Applicants respectfully traverse the foregoing rejections under 35 U.S.C. §102 and request reconsideration and withdrawal of the rejections. As stated above, for a prior art reference to anticipate a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. In contrast to all of the references relied upon by the Examiner, the currently pending claims are directed to ***a method for protecting a mature T cell from cell death...wherein the agent increases BCL-X_L protein level.***

Groux, *et al.* teach that anti-CD28 prevents PBMC stimulated with PVM ***or*** SEB from HIV infected individuals from undergoing activation induced T cell death. However, a ***proliferative*** amount of anti-CD3 was required in these conditions to inhibit AICD (page 337, left-hand column, first paragraph and the second paragraph on the left-hand side of page 333 which states that ***"[p]roliferation*** of T cells from HIV-infected individuals to Con A and to CD3 mAB was only slightly reduced" indicating that control cells as well as HIV-infected cells were treated with a ***mitogenic*** amount of anti-CD3).

Wolf, *et al.* teach at page 1412 Section 3.2 that "[s]timulation with a ***mitogenic*** concentration of anti-CD3 (1mg/ml) plus a costimulus induced vigorous ***cell proliferation***".

With respect to Lederman, *et al.* and the Thompson, *et al.* references, these references teach the identification of a monoclonal antibody (5c8) that ***inhibits T cell activation*** of B cells and methods of ***inhibiting an autoimmune response*** utilizing the antibody (see abstract and claims).

Gary, *et al.* teach methods that enable the "selective stimulation of a T cell population to proliferate and expand to significant numbers ***in vitro in the absence of exogenous growth factors or accessory cells.***" (column 4, lines 30-33).

The currently pending claims are directed to ***a method for protecting a mature T cell from cell death...wherein the agent increases BCL-X_L protein level***. None of the above cited references teach ***a method of protecting a mature T cell from death, wherein the agent increases BCL-X_L protein level***, let alone the specific agents, as presently claimed. These references therefore can not, and do not, anticipate the present claims.

With respect to the 35 U.S.C. §102(f) rejections, Applicants submit that none of the references cited by the Examiner teach each and every element of the claimed methods, and therefore, the rejection is inappropriate. Applicants further submit that the inventorship of the instant application is correct. Applicants therefore request withdrawal of the rejection.

Rejection of Claims 1 and 34 and 38 Under 35 U.S.C. §103

Applicants note the withdrawal of the rejection of claim 1, 34, and 38 under 35 U.S.C. §103 as being unpatentable over Leonardo, *et al.* (US 6,083,503) in view of Roberts, *et al.* (US 5,686,281).

Double Patenting

The Examiner has rejected claims 1, 32-35, 37, and 38 under the judicially created doctrine of obviousness-type double patenting as being "unpatentable over claims 1, 15-19, 31, and 32 of U.S. Patent No. 6,352,694 (June, *et al.*). The Examiner states that "because the submitogenic amount is fully disclosed in the cited patent, the rejection stands."

The Examiner has rejected claims 1, 32-35, and 38 under the judicially created doctrine of obviousness-type double patenting as being "unpatentable over claims 1-12 of U.S. Patent No. 6,534,055 (June, *et al.*). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims of the present application and claims of the cited patent are each drawn to a method comprising the steps of contacting the T cell with two agents selected from the group consisting of anti-CD3 antibody, anti-CD28 antibody, a CD28 ligand, and IL-2."

The Examiner continues "[t]he processes of the present application and the cited patent differ one from the other in the preamble recitations, however, the recitations "for expanding a population of T cells" or "for preparing a renewable source of T cells" in the cited patent or "for

protecting a T cell from cell death" in the present application are obvious variants, i.e. maintaining a T cell population in culture."

Applicants respectfully traverse these rejections and reiterate that protection from apoptosis is not necessarily coincident with induction of cell proliferation, and likewise, a culture which is not proliferating is not undergoing apoptosis. Simply because a cell is not proliferating does not mean that it automatically proceedes to apoptosis. Apoptosis by definition is an active event that requires multiple genes to be turned on and in order for those genes to be turned on, there must be an initiating cellular signal. Applicants have identified a function of anti-CD3 in T cells which is independent of its proliferative activity. In Example 1 of the instant application, Applicants show that use of a submitogenic amount of an anti-CD3 antibody is sufficient for protection from programmed cell death, but not sufficient to induce proliferation upon costimulation. Applicants again refer the Examiner to Example 1, page 34, line 25- which reads:

> ***The maintenance of cell viability in anti-CD3 stimulated and anti-CD3 + anti-CD28 stimulated cells was not the result of subsequent T cell proliferation*** as cell counts done in parallel to the viability assays revealed that the absolute cell number did not change. Furthermore, all the cells in the activated populations were arrested within the cell cycle at either late G1 or G2. (emphasis added)

The protective activity of anti-CD3 is therefore separable from the proliferative activity of anti-CD3. Moreover, claims 1 and 39 require a ***submitogenic*** amount of anti-CD3 antibody which is not taught or suggested by the references relied upon by the Examiner. Applicants therefore request withdrawal of the rejection.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

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Respectfully submitted,

By _____

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